REMARKS

Reconsideration is respectfully requested.

First of all, the Examiner is respectfully requested to note the subject matter of the claims as now submitted, being claims 9-20. Claims 9 and 15 are generic thrombin-containing composition claims, with claim 9 reciting presence of a stabilization amount of a surfactant and/or gelatin, while claim 15 recites the presence of a stabilizer combination of Ca ion with a water-soluble organic acid. Generic method of stabilization claims 18 and 20 basically correspond in subject matter to composition claims 9 and 15 with respect to the stabilizers used.

First of all, Applicants respectfully request acknowledgement of their claim to priority. Applicants confirm their previous election.

Applicants note that with respect to the Information Disclosure Statement submitted on March 27, 2002, from a copy of cited prior art listing returned by the Examiner with the outstanding Office Action that no consideration has been given to EP 004799, although Applicants have cited therewith the International Search Report indicating the degree of relevance thereof. Examiner is at least respectfully requested to indicate consideration of said reference to the extent as to its relevance in accordance with the International Search Report.

Applicants now turn to consideration of the prior art rejections.

At the top of page 3 of the Office Action, claims 1-3 are rejected under 35 U.S.C. § 102(e) as being anticipated by Mosesson et al. The Examiner cites Mosesson et al. as teaching a combination of calcium chloride and acetic acid. In view thereof, it is expected at this present time the Examiner would consider Mosesson et al. is relevant to generic claim 15 directed to the use of Ca ion in combination with a water soluble organic acid to stabilize thrombin.

Mosesson et al. disclose a thrombin inhibitor comprising a means for inactivating or sequestering thrombin and a portion of the fibrinogen γ' chain that binds at the anion-binding exosite of thrombin (column 3, lines 23-26).

The Examiner has misinterpreted the Mosesson et al. reference. Mosesson et al. describe a thrombin-fibrin binding experiment, including steps of preparing a 10 mg/ml fibrin stock solution and conducting a binding analysis. The fibrin solution is prepared by: (1) clotting fibrinogen with thrombin; (2) synerizing and dissolving the clots in acetic acid; (3) repolymerizing the fibrin monomer solutions in a buffer containing $CaCl_2$; and (4) synerizing and dissolving the clots in acetic acid (column 8, lines 16-26). Clot-bound thrombin is formed by adding the fibrin solution to a solution containing thrombin (column 8, lines 26-32).

Based on the disclosure of Mosesson et al., in the first step, thrombin binds fibrinogen and cleaves it to fibrin clots, and there is at most an insignificant amount of thrombin in the clots. Accordingly, it would seem that, thrombin is not present in the fibrin solution obtained thereafter when acetic acid is used or in the repolymerization step when calcium chloride is used.

Therefore, Mosesson et al. do not teach a composition containing both thrombin, acetic acid and calcium ion. Even if thrombin is coexistent with calcium ion at one point, the presence of calcium ion does not appear to provide a means to stabilize thrombin, because thrombin would likely bind fibrin and/or its polymer (thrombin is known to bind fibrin, see column 1, lines 44-45 of Mosesson et al.). Accordingly, Mosesson et al. do not anticipate claims 1 and 3.

Next, claims 1-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Baumbach et al. The Examiner refers to Example 3 as teaching thrombin, $CaCl_2$, PEG and a buffer, plus the

reference according to the Examiner also teaches acetic acid. It is expected that the Examiner will now consider this rejection as relevant to generic claim 15. As explained below, Baumbach et al. never teaches nor suggests the combination of a calcium ion with a water-soluble organic acid in the presence of thrombin.

Baumbach et al. disclose a method of purifying prothrombin and thrombin in an affinity process using peptides which have the ability to bind prothrombin and thrombin (column 2, lines 34-44). The method comprises: (1) activating a sample of prothrombin complex concentrate (PTC) in the presence of $CaCl_2$; (2) injecting the activated PTC eluate onto a column of peptide resin; (3) washing the column with equilibration buffer containing HEPES, $CaCl_2$, NaCl and PEG; (4) washing the column with sodium citrate to release thrombin; and (5) washing the column with acetic acid to remove remaining protein (Example 3).

Baumbach et al. do not teach a means for stabilizing thrombin as presently claimed for the following reasons. First, in the first step, $CaCl_2$ is used for the purposes of activating PTC eluate to form thrombin (column 8, lines 17-18). Second, the equilibration buffer appears to release a portion of bound protein (thrombin). Third, acetic acid is used to remove any remaining protein bound to the column (column 8, lines 25-26). Furthermore, Baumbach et al. do not teach the combination use of $CaCl_2$ and acetic acid. Accordingly, Baumbach et al. do not anticipate the subject matter of present claims.

Next, claims 4-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hemker, Uriyu et al., Ogawa, et al., Winant et al., or JP '369. The Examiner submits that the references teach thrombin, calcium chloride, PEG, organic acids and buffers.

Hemker discloses, in the Example, a step of incubation of patient plasma samples with a preparation containing bovine Factor XIa, bovine thrombin, calcium chloride, phospholipids, tris-(hydroxymethyl)-aminomethane (Tris) buffer, and stabilizers BSA and polyethylene glycol 6000, and a step of addition of a quenching substance comprising Tris buffer, ethylenediaminetetracetic acid, sodium chloride and sodium azide (column 5, lines 26-45).

It appears to us that Hemker teach a composition comprising thrombin, calcium ion, protein and PEG. However, acetic acid is used as a quenching component instead of a stabilizing agent. In addition, Hemker does not teach use of a surfactant.

From the above, Applicants submit that Hemker does not teach a composition anticipating claim 9 or 15, since Hemker does not disclose surfactant or gelatin, nor calcium plus water-soluble organic acid with the thrombin.

Uriyu et al. disclose a liquid preparation of antithrombin-III and stabilizing method (abstract). Uriyu et al. disclose use of a human thrombin solution which comprises sodium chloride, BSA, PEG 6000 and thrombin (column 9, lines 3-6). Uriyu et al. also disclose that a citric acid solution is used to stop a reaction (column 9, lines 11-12).

Uriyu et al. teach a solution comprising thrombin, protein and PEG. However, Uriyu et al. do not teach use of calcium ion and surfactant. Citric acid is not present in the original thrombin-containing solution of Uriyu et al., but is added to a mixture to stop a reaction. Therefore, Uriyu et al. do not teach the combination use of calcium and an acid.

From the above, Uriyu et al. do not suggest stabilization effect for thrombin of surfactant or gelatin, nor a combination of calcium ion with the water-soluble organic acid.

Ogawa et al teach a method for measuring the activity of plasma factor XIII (abstract). Ogawa et al disclose that plasma factor XIII, a non-active enzyme, is converted into its active form XIIIa by the action of thrombin and Ca ion in plasma (column 1, lines 15-19), wherein the thrombin buffer solution comprises BSA.

Thrombin reacts with plasma factor XIII in the presence of Ca ion in Ogawa et al. Accordingly, there is no free thrombin in the mixture. Therefore, Ogawa et al do not teach a composition containing thrombin.

Winant et al teach production and use of amino acid substituted hirudin polypeptides as antithrombotic agent (column 1, lines 5-10 and abstract). Winant et al disclose that in a clotting assay, a buffer solution containing thrombin, PEG and calcium chloride is used (column 8, lines 56-60), and in a chromogenic assay, hirudin is mixed with thrombin and PEG (column 8, lines 33-42). However, Winant et al do not teach use of a surfactant, gelatin or calcium ion plus water-soluble organic acid in a thrombin-containing solution.

The JP '369 reference discloses a thrombolytic agent comprising a PEG, thrombin, and heavy metal. Heavy metal is used as contrast medium; the reference is silent about an effect of stabilizing thrombin. And also, gold, silver, bismuth, or thorium is the heavy metal. Calcium is not disclosed as the heavy metal example.

From the above, Applicants respectfully submit that all of the anticipatory rejections should be reconsidered and withdrawn.

Next, Applicants turn to the 35 U.S.C. § 103(a) rejections.

Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Mosesson et al. Applicants respectfully submit that prima facia case of obviousness has not been presented in view of the comments set forth above concerning this reference. There is no teaching or suggestion in the reference of employment of a surfactant or gelatin, or calcium ion plus water-soluble organic acid to stabilize thrombin.

At the top of page 4 of the Office Action, claims 1-6 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Baumbach et al. Again, the stabilizers of claims 9 and 15 are not suggested nor taught by this reference, and, accordingly, it cannot present a prima facia case of obviousness. Please see further discussion of this reference with respect to the anticipatory rejection noted above.

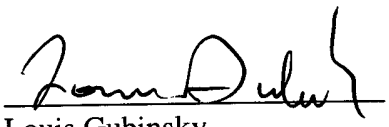
At the middle of page 4 of the Office Action, claims 4-6 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hemker, Uriyu et al., Ogawa, et al., Winant et al. or JP '369.

Each of these references has been discussed in detailed above with respect to its disclosures which could possibly be relevant to the present invention. Applicants have established herein above that none of these references teach or suggest the stabilizers of claims 9 and 15 for use in stabilization of thrombin. Accordingly, Applicants submit that all of their claims are unobvious over the references applied of Hemker, Uriyu et al., Ogawa, et al., Winant et al. or JP '369.

Early indication of allowability is respectfully requested. If any minor points remain prior to notice of allowance, the Examiner is respectfully requested to contact the undersigned at the below listed phone number.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Louis Gubinsky
Registration No. 24,835

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE

23373
PATENT TRADEMARK OFFICE

Date: March 5, 2003

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The specification is changed as follows:

Amend the specification by inserting before the first line the sentence:

This Application is a National Stage Entry of PCT JP00/06513, filed September 22, 2000, claiming priority from Japanese Application Nos. HE11-272092, filed September 27, 1999 and JP2000-212924, filed July 13, 2000.

IN THE CLAIMS:

Cancel all claims, substituting therefore the following claims 9-20.

Claims 9-20 are added as new claims.